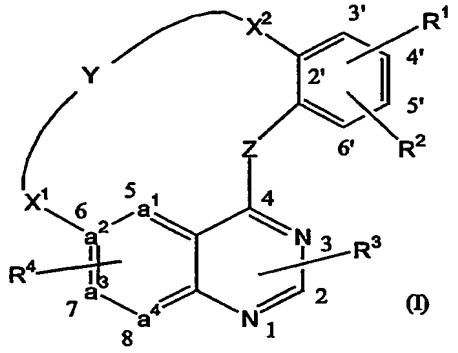
Claims

1. A compound having the formula



(I)

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

a^1-a^2=a^3-a^4 represents a divalent radical selected from N-CH=CH-CH, N-CH=N-CH or CH-CH=N-CH;

Z represents O, NH or S;

Y represents -C_{3-9}alkyl-, -C_{3-9}alkenyl-, -C_{1-5}alkyl-oxy-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{14}-CO-C_{1-5}alkyl-, -C_{1-5}alkyl-CO-NR^{15}-C_{1-5}alkyl-, -C_{1-6}alkyl-CO-NH-, -C_{1-6}alkyl-NH-CO-, -CO-NH-C_{1-6}alkyl-, -NH-CO-C_{1-6}alkyl-, -CO-C_{1-7}alkyl-, -C_{1-7}alkyl-CO-, C_{1-6}alkyl-CO-C_{1-6}alkyl;

X^1 represents a direct bond, O, -O-C_{1-2}alkyl-, CO, -CO- C_{1-2}alkyl-, NR^{11}, -NR^{11}-C_{1-2}alkyl-, NR^{16}-CO-, NR^{16}-CO-C_{1-2}alkyl-, -O-N=CH- or C_{1-2}alkyl;

X^2 represents a direct bond, O, -O-C_{1-2}alkyl-, CO, -CO- C_{1-2}alkyl-, NR^{12}, NR^{12}-C_{1-2}alkyl-, NR^{17}-CO-, NR^{17}-CO-C_{1-2}alkyl-, Het^{20}-C_{1-2}alkyl-, -O-N=CH- or C_{1-2}alkyl;

R^1 represents hydrogen, cyano, halo, hydroxy, formyl, C_{1-6}alkoxy-, C_{1-6}alkyl-, C_{1-6}alkoxy- substituted with halo,
C_{1-4}alkyl substituted with one or where possible two or more substituents selected from hydroxy or halo;

R^2 represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-, Het^{16}-carbonyl-, C_{1-4}alkyloxycarbonyl-, C_{1-4}alkylcarbonyl-, aminocarbonyl-, mono-or di(C_{1-4}alkyl)aminocarbonyl-, Het^1, formyl, C_{1-4}alkyl-, C_{2-6}alkynyl-, C_{3-6}cycloalkyl-, C_{3-6}cycloalkyloxy-, C_{1-6}alkoxy-, Ar^5, Ar^1-oxy-, dihydroxyborane , C_{1-6}alkoxy- substituted with halo,

C_{1-4}alkyl substituted with one or where possible two or more substituents selected from halo, hydroxy or NR^5R^6,

C_{1-4}alkylcarbonyl- wherein said C_{1-4}alkyl is optionally substituted with one or where possible two or more substituents selected from hydroxy or C_{1-4}alkyl-oxy-;

R^3 represents hydrogen, C_{1-4}alkyl, cyano or C_{1-4}alkyl substituted with one or more substituents selected from halo, C_{1-4}alkyloxy-, amino-, mono-or di(C_{1-4}alkyl)amino-, C_{1-4}alkyl-sulfonyl- or phenyl;

R^4 represents hydrogen, hydroxy, Ar^3-oxy, Ar^4-C_{1-4}alkyloxy-, C_{1-4}alkyloxy-, C_{2-4}alkenyloxy- optionally substituted with Het^{12} or R^4 represents C_{1-4}alkyloxy substituted with one or where possible two or more substituents selected from C_{1-4}alkyloxy-, hydroxy, halo, Het^2-, -NR^7R^8, -carbonyl- NR^9R^{10} or Het^3-carbonyl-;

R^5 and R^6 are each independently selected from hydrogen or C_{1-4}alkyl;

R^7 and R^8 are each independently selected from hydrogen, C_{1-4}alkyl, Het^8, aminosulfonyl-, mono- or di (C_{1-4}alkyl)-aminosulfonyl, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyl-oxy-C_{1-4}alkyl-, hydroxycarbonyl-C_{1-4}alkyl-, C_{3-6}cycloalkyl, Het^9-carbonyl-C_{1-4}alkyl-, Het^{10}-carbonyl-, polyhydroxy-C_{1-4}alkyl-, Het^{11}-C_{1-4}alkyl- or Ar^2-C_{1-4}alkyl-;

R^9 and R^{10} are each independently selected from hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, Het^4, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyloxyC_{1-4}alkyl- or polyhydroxy-C_{1-4}alkyl-;

R^{11} represents hydrogen, C_{1-4}alkyl, Het^5, Het^6-C_{1-4}alkyl-, C_{2-4}alkenylcarbonyl- optionally substituted with Het^7-C_{1-4}alkylaminocarbonyl-, C_{2-4}alkenylsulfonyl-, C_{1-4}alkyloxyC_{1-4}alkyl- or phenyl optionally substituted with one or where possible two or more substituents selected from hydrogen, hydroxy, amino or C_{1-4}alkyloxy-;

R^{12} represents hydrogen, C_{1-4}alkyl, C_{1-4}alkyl-oxy-carbonyl-, Het^{17}, Het^{18}-C_{1-4}alkyl-, C_{2-4}alkenylcarbonyl- optionally substituted with Het^{19}-C_{1-4}alkylaminocarbonyl-, C_{2-4}alkenylsulfonyl-, C_{1-4}alkyloxyC_{1-4}alkyl- or phenyl optionally substituted with one or where possible two or more substituents selected from hydrogen, hydroxy, amino or C_{1-4}alkyloxy-;

R^{13} represents hydrogen, C_{1-4}alkyl, Het^{13}, Het^{14}-C_{1-4}alkyl- or phenyl optionally substituted with one or where possible two or more substituents selected from hydrogen, hydroxy, amino or C_{1-4}alkyloxy-;

R^{14} and R^{15} are each independently selected from hydrogen, C_{1-4}alkyl, Het^{15}-C_{1-4}alkyl- or C_{1-4}alkyloxyC_{1-4}alkyl-;

R^{16} and R^{17} are each independently selected from hydrogen, C_{1-4}alkyl, Het^{21}-C_{1-4}alkyl- or C_{1-4}alkyloxyC_{1-4}alkyl-;

Het^1 represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het^1 is optionally substituted with one or where possible two or more substituents selected from amino, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl-, phenyl, phenyl-C_{1-4}alkyl-, C_{1-4}alkyl-oxy-C_{1-4}alkyl- mono- or di(C_{1-4}alkyl)amino- or amino-carbonyl-;

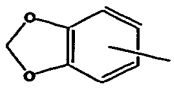
Het^2 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, thiomorpholinyl or dithianyl wherein said Het^2 is optionally substituted with one or where possible two or more substituents selected from hydroxy, halo, amino, C_{1-4}alkyl-, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyl-oxy-C_{1-4}alkyl-, hydroxy-C_{1-4}alkyl-oxy-C_{1-4}alkyl-, mono- or di(C_{1-4}alkyl)amino-, mono- or di(C_{1-4}alkyl)amino-C_{1-4}alkyl-, aminoC_{1-4}alkyl-, mono- or di(C_{1-4}alkyl)amino-sulfonyl-, aminosulfonyl-;

Het^3, Het^4 and Het^8 each independently represent a heterocycle selected from morpholinyl, piperazinyl, piperidinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het^3, Het^4 or Het^8 is optionally substituted with one or where possible two or more substituents selected from hydroxy-, amino-, C_{1-4}alkyl-, C_{3-6}cycloalkyl-C_{1-4}alkyl-, aminosulfonyl-, mono- or di(C_{1-4}alkyl)aminosulfonyl or amino-C_{1-4}alkyl-;

Het^5 represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said heterocycle is optionally substituted with one or where possible two or more substituents selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyloxyC_{1-4}alkyl or polyhydroxy-C_{1-4}alkyl-;

Het^6 and Het^7 each independently represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het^6 and Het^7 are optionally substituted with one or where possible two or more substituents selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyloxyC_{1-4}alkyl or polyhydroxy-C_{1-4}alkyl-;

Het^9 and Het^{10} each independently represent a heterocycle selected from furanyl, piperidinyl, morpholinyl, piperazinyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het^9 or Het^{10} is optionally substituted C_{1-4}alkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl- or amino-C_{1-4}alkyl-;

Het^{11} represents a heterocycle selected from indolyl or  ;

Het^{12} represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, thiomorpholinyl or dithianyl wherein said Het^{12} is optionally substituted with one or where possible two or more substituents selected from hydroxy, halo, amino, C_{1-4}alkyl-, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyl-oxy-C_{1-4}alkyl-, hydroxy-C_{1-4}alkyl-oxy-C_{1-4}alkyl-, mono- or di(C_{1-4}alkyl)amino- or mono- or di(C_{1-4}alkyl)amino-C_{1-4}alkyl-;

Het^{13} represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said heterocycle is optionally substituted with one or where possible two or more substituents selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, hydroxy-C_{1-4}allkyl-, C_{1-4}alkyloxyC_{1-4}alkyl or polyhydroxy-C_{1-4}alkyl-;

Het^{14} represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said heterocycle is optionally substituted with one or where possible two or more substituents selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyloxyC_{1-4}alkyl or polyhydroxy-C_{1-4}alkyl-;

Het^{15} and Het^{21} each independently represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het^{15} or Het^{21} are optionally substituted with one or where possible two or more substituents selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyloxyC_{1-4}alkyl or polyhydroxy-C_{1-4}alkyl-;

Het^{16} represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl, 1,3,2-dioxaborolane or piperidinyl wherein said heterocycle is optionally substituted with one or more substituents selected from C_{1-4}alkyl;

Het^{17} represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said heterocycle is optionally substituted with one or where possible two or more substituents selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyloxyC_{1-4}alkyl or polyhydroxy-C_{1-4}alkyl-;

Het^{18} and Het^{19} each independently represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het^{18} and Het^{19} are optionally substituted with one or where possible two or more substituents selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyloxyC_{1-4}alkyl or polyhydroxy-C_{1-4}alkyl-;

Het^{20} represents a heterocycle selected from pyrrolidinyl, 2-pyrrolidinyl, piperidinyl, piperazinyl or pyrazolidinyl wherein said heterocycle is optionally substituted with one or where possible two or more substituents selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyloxyC_{1-4}alkyl or polyhydroxy-C_{1-4}alkyl-; and

Ar^1, Ar^2, Ar^3, Ar^4 and Ar^5 each independently represent phenyl optionally substituted with cyano, C_{1-4}alkylsulfonyl-, C_{1-4}alkylsulfonylamino-, aminosulfonylamino-, hydroxy-C_{1-4}alkyl, aminosulfonyl-, hydroxy-, C_{1-4}alkyloxy- or C_{1-4}alkyl.

2. A compound according to claim 1 wherein;

Z represents NH;

Y represents -C_{3-9}alkyl-, -C_{2-9}alkenyl-, -C_{1-5}alkyl-oxy-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{14}-CO-C_{1-5}alkyl-, -C_{1-6}alkyl-NH-CO-, -CO-C_{1-7}alkyl-, -C_{1-7}alkyl-CO- or C_{1-6}alkyl-CO-C_{1-6}alkyl;

X^1 represents O, -O-C_{1-2}alkyl-, -O-N=CH-, NR^{11} or -NR^{11}-C_{1-2}alkyl-; in a particular embodiment X^1 represents a direct bond, C_{1-2}alkyl-, -O-C_{1-2}alkyl,-NR^{11}-, –O- or –O-CH_2-;

X^2 represents a direct bond, O, -O-C_{1-2}alkyl-, -O-N=CH-, NR^{17}-CO-, NR^{17}-CO-C_{1-2}alkyl-, C_{1-2}alkyl, Het^{20}-C_{1-2}alkyl-, NR^{12} or NR^{12}-C_{1-2}alkyl-; in a particular embodiment X^2 represents a direct bond, C_{1-2}alkyl-, -O-C_{1-2}alkyl, NR^{17}-CO-, NR^{17}-CO-C_{1-2}alkyl-, Het^{20}-C_{1-2}alkyl-, –O- or –O-CH_2-;

R^1 represents hydrogen, cyano, halo or hydroxy, preferably halo;

R^2 represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-, C_{1-4}alkyloxycarbonyl-, Het^{16}-carbonyl-, C_{1-4}alkyl-, C_{2-6}alkynyl-, Ar^5 or Het^1; in a further embodiment R^2 represents hydrogen, cyano, halo, hydroxy, or Ar^5; in a more particular embodiment R^2 represents hydrogen or halo;

R^3 represents hydrogen;

R^4 represents hydrogen, hydroxy, C_{1-4}alkyloxy-, Ar^4-C_{1-4}alkyloxy or R^4 represents C_{1-4}alkyloxy substituted with one or where possible two or more substituents selected from C_{1-4}alkyloxy- or Het^2-;

R^{11} represents hydrogen, C_{1-4}alkyl- or C_{1-4}alkyl-oxy-carbonyl-;

R^{12} represents hydrogen, C_{1-4}alkyl- or C_{1-4}alkyl-oxy-carbonyl-;

R^{13} represents hydrogen or Het^{14}-C_{1-4}alkyl, in particular morpholinyl-C_{1-4}alkyl;

R^{14} represents hydrogen or C_{1-4}alkyl;

R^{17} represents hydrogen, C_{1-4}alkyl-, Het^{21}-C_{1-4}alkyl or C_{1-4}alkyl-oxy-C_{1-4}alkyl; in particular R^{17} represents hydrogen or C_{1-4}alkyl;

Het^1 represents thiazolyl optionally substituted with amino, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl-, phenyl, phenyl-C_{1-4}alkyl-, C_{1-4}alkyl-oxy-C_{1-4}alkyl-, mono- or di(C_{1-4}alkyl)amino- or amino-carbonyl-;

Het^2 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl wherein said Het^2 is optionally substituted with one or where possible two or more substituents selected from hydroxy, amino or C_{1-4}alkyl-;
In a further embodiment Het^2 represents a heterocycle selected from morpholinyl or piperidinyl optionally substituted with C_{1-4}alkyl-, preferably methyl;
Het^{14} represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl wherein said Het^{14} is optionally substituted with one or where possible two or more substituents selected from hydroxy, amino or C_{1-4}alkyl-;
Het^{16} represents a heterocycle selected from piperidinyl, morpholinyl or pyrrolidinyl;
Het^{20} represents a heterocycle selected from pyrrolidinyl, 2-pyrrolidinyl or piperidinyl;
Het^{21} represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl wherein said Het^{21} is optionally substituted with one or where possible two or more substituents selected from hydroxy, amino or C_{1-4}alkyl-;
Ar^4 represents phenyl optionally substituted with cyano, hydroxy-, C_{1-4}alkyloxy or C_{1-4}alkyl;
Ar^5 represents phenyl optionally substituted with cyano, hydroxy, C_{1-4}alkyloxy or C_{1-4}alkyl.

3. A compound according to claim 1 wherein;
Z represents NH;
Y represents -C_{3-9}alkyl-, -C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{14}-CO-C_{1-5}alkyl-, -C_{1-6}alkyl-NH-CO- or
-CO-NH -C_{1-6}alkyl- ;
X^1 represents -O-, -NR^{11}-, -NR^{16}-CO-, or -NR^{16}-CO-C_{1-2}alkyl-;
X^2 represents a direct bond, -C_{1-2}alkyl-, -O-C_{1-2}alkyl, -O-, –O-CH_2- or Het^{20}-C_{1-2}alkyl-;
R^1 represents hydrogen or halo;
R^2 represents hydrogen, cyano, halo, hydroxycarbonyl-, C_{1-4}alkyloxycarbonyl-, Het^{16}-carbonyl- or Ar^5; in particular R^2 represents hydrogen or halo;
R^3 represents hydrogen;
R^4 represents hydrogen, hydroxy, C_{1-4}alkyloxy-, Ar^4-C_{1-4}alkyloxy or R^4 represents C_{1-4}alkyloxy substituted with one or where possible two or more substituents selected from
C_{1-4}alkyloxy- or Het^2-;
R^{11} represents hydrogen;
R^{12} represents hydrogen, C_{1-4}alkyl- or C_{1-4}alkyl-oxy-carbonyl-;
R^{13} represents hydrogen or Het^{14}-C_{1-4}alkyl, in particular hydrogen or morpholinyl-C_{1-4}alkyl;

Het^2 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl wherein said Het^2 is optionally substituted with one or where possible two or more substituents selected from hydroxy, amino or C_{1-4}alkyl-;
In a further embodiment Het^2 represents a heterocycle selected from morpholinyl or piperidinyl optionally substituted with C_{1-4}alkyl-, preferably methyl;
Het^{14} represents morpholinyl;
Het^{16} represents a heterocycle selected from morpholinyl or pyrrolidinyl;
Het^{20} represents pyrrolidinyl or piperidinyl;
Ar^4 represents phenyl;
Ar^5 represents phenyl optionally substituted with cyano.

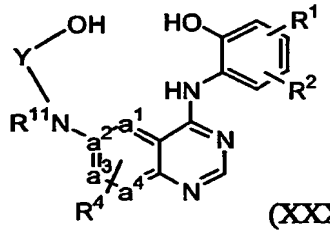
4. A compound according to claim 1 or 2 wherein the R^1 substituent is at position 4', the R^2 substituent is at position 5', the R^3 substituent is at position 3 and the R^4 substituent at position 7 of the structure of formula (I).

5. A compound according to any one of claims 1 to 4 wherein a^1-a^2=a^3-a^4 represents N-CH=CH-CH.

6. A compound according to any one of claims 1 to 4 wherein a^1-a^2=a^3-a^4 represents N-CH=N-CH.

7. A compound according to any one of claims 1 to 4 wherein a^1-a^2=a^3-a^4 represents CH-CH=N-CH.

8. An intermediate of formula



(XXXI)

the N-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein
a^1-a^2=a^3-a^4 represents a divalent radical selected from N-CH=CH-CH or N-CH=N-CH;
Y represents -C_{3-9}alkyl-, -C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl-, -C_{1-6}alkyl-NH-CO- or -CO-NH -C_{1-6}alkyl- ;
R^1 represents hydrogen or halo;

R^2 represents hydrogen, cyano, halo, hydroxycarbonyl-, C_{1-4}alkyloxycarbonyl-, Het^{16}-carbonyl- or Ar^5;

R^4 represents hydroxy, C_{1-4}alkyloxy-, Ar^4-C_{1-4}alkyloxy or R^4 represents C_{1-4}alkyloxy substituted with one or where possible two or more substituents selected from C_{1-4}alkyloxy- or Het^2-;

R^{11} represents hydrogen;

R^{13} represents Het^{14}-C_{1-4}alkyl;

Het^2 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl wherein said Het^2 is optionally substituted with one or where possible two or more substituents selected from hydroxy, amino or C_{1-4}alkyl-;

Het^{14} represents morpholinyl;

Het^{16} represents a heterocycle selected from morpholinyl or pyrrolidinyl;

Ar^4 represents phenyl;

Ar^5 represents phenyl optionally substituted with cyano.

9. A kinase inhibitor of formula (I) or formula (XXXI).

10. A compound as claimed in any one of claims 1 to 7 for use as a medicine.

11. Use of a compound as claimed in any one of claims 1 to 7 in the manufacture of a medicament for treating cell proliferative disorders such as atherosclerosis, restenosis and cancer.

12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, an effective kinase inhibitory amount of a compound as described in any one of the claims 1 to 7.

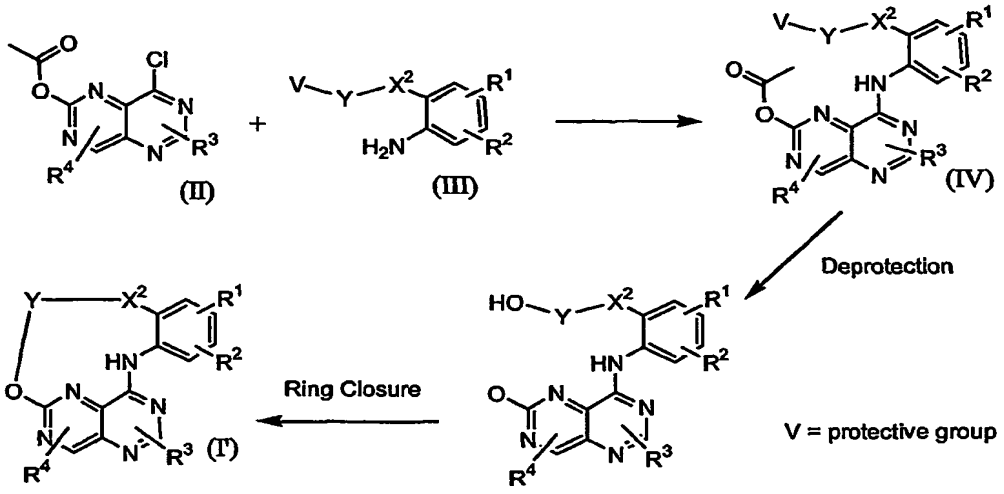
13. An intermediate as claimed in claim 8 for use as a medicine.

14. Use of an intermediate as claimed in claim 8 in the manufacture of a medicament for treating cell proliferative disorders such as atherosclerosis, restinosis and cancer.

15. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, an effective kinase inhibitory amount of an intermediate as claimed in claim 6.

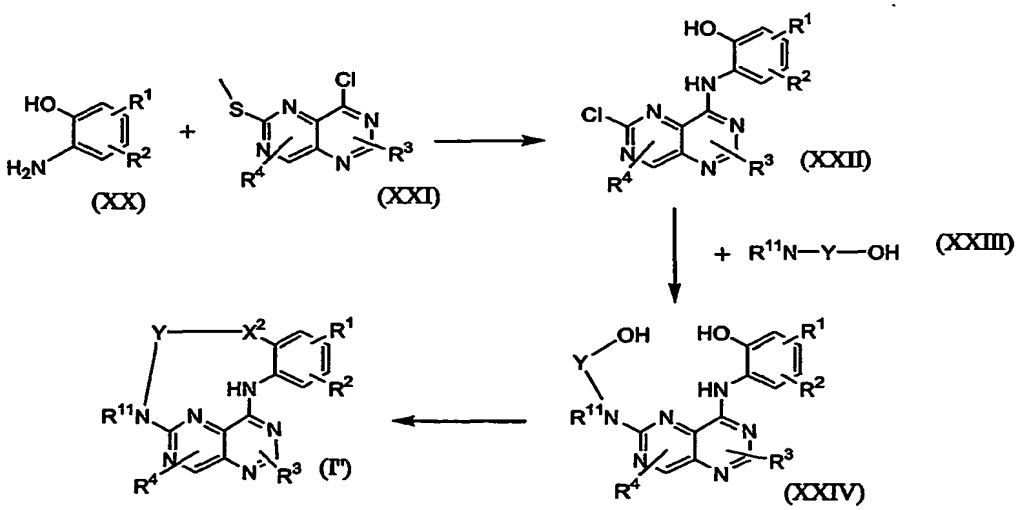
16. A process for preparing a compound as claimed in claims 1 to 7, comprising;

a) coupling 2-acetoxy-8-chloropyrimido[5,4-d]pyrimidine derivatives (II) with suitable substituted anilines (III), to furnish the intermediates of formula (IV), and deprotecting the intermediates of formula (IV) followed by ring closure under suitable conditions.



; or

b) coupling the known 8-chloro-2(methylthio)-pyrimido[5,4-d]pyrimidine with 2-aminophenol derivatives of formula (XXI), yielding the intermediate compounds of formula (XXII). Next, the pyrido[3,2-d]pyrimidine of formula (XXII) is aminated using an aminated alcohol (XXIII) under art known conditions, followed by ring closure under Mitsunobu conditions to give the target compounds of formula (I'')



17. A method of treating a cell proliferative disorder, the method comprising administering to an animal in need of such treatment a therapeutically effective amount of a compound as claimed in any one of claims 1 to 7.

18. A method of treating a cell proliferative disorder, the method comprising administering to an animal in need of such treatment a therapeutically effective amount of an intermediate as claimed in claim 8.